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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,220	06/17/2005	Nicola Murdoch Heron	100938-1P US	4585

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EXAMINER
TRUONG, TAMTHOM NGO

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
04/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,220	HERON ET AL.	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10-04-05 (Pre. Amdt)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 18-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *12 and 25* is/are allowed.

6)☒ Claim(s) *1-10,13 and 18-21* is/are rejected.

7)☒ Claim(s) *11 and 22-24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/15/08, 10/4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment of 10-04-05 is acknowledged.

Claims 14-17 are cancelled.

Claims 21-25 have been added.

Therefore, pending claims are 1-13 and 18-25.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Scope of Enablement:** Claims 18, 19 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of colorectal cancer, does not reasonably provide enablement for the treatment of other cancers, or diseases related to Aurora kinases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 18 recites "a method of treating a human suffering from a disease in which the inhibition of one or more Aurora kinases is beneficial," which covers "a hyperproliferative disease such as cancer and in particular … colorectal, breast, lung, prostate, pancreatic or bladder and renal cancer or leukemias or lymphomas". However, all those cancers affect different organs, and have different manifestation as well as different rate of metastasis. Furthermore, there are various types of cancers within a group. For examples, lung cancer includes mesothelioma, non-small cell lung cancer and small-cell lung cancer, the latter of which spreads quickly, and is quite difficult to treat. Likewise, there are several types of leukemias and lymphomas. Claim 21 depends on claim 18, and thus, carries the same broad scope.

Claim 19 recites a method of treating specific cancers, but still includes several cancers affecting different organs. Thus, the scopes of claims 18 and 19 are unduly broad.

The amount of direction or guidance presented: The specification describes two *in-vitro* assays, but only uses colorectal cell line (SW 620 (ATCC CCL-227). Due to dissimilar morphology, the data for colorectal cell line cannot be extrapolated to other cell lines such as: breast, lung, renal, pancreatic, prostate, etc. Thus, the specification fails to provide sufficient

enablement for treating various cancers or diseases related to Aurora kinase other than treating colorectal cancer.

The state of the prior art: Although quinazoline compounds are known to treat cancers, it is still a challenge to treat many cancers such as small-cell lung cancer, leukemias, lymphomas, pancreatic or renal cancer. Each type of cancer metastasizes at a different rate and may or may not respond to certain drugs. Therefore, the *in-vitro* model for one cell line cannot predict the activity for other cell lines as according to **Voskoglou-Nomikos et. al.**, which discloses that not all *in-vitro* models are predictable for various types of cancers (e.g., see the abstract on page 4227). Thus, the state of the art does not support the treatment of several cancers based on the *in-vitro* model of only one cell line.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of formula I. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Given a large Markush group of the claimed formula I, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the *in-vitro* activity for a colorectal cell line does not allow a clinician to predict efficacy and safety to treat other cancers using the claimed compounds.

See ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Thus, given the unpredictable nature of the art, and the vast number of compounds claimed herein, one skilled in the art will have to carry out undue experimentation to practice the method of treatment recited in claims 18, 19 and 21.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-10, 13 and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claim 1 recites the definition of R^3 to include "C_{1-6} alkoxy" and "-OR^{12}". Variable R^{12} is defined as C_{1-4} alkyl. Thus, the definition of R^3 has a broad limitation followed by a narrow limitation.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. &

Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

b. Claim 20 recites the phrase "converting a compound of formula (I) into another compound of formula (I)" which is unclear as to which compound gets converted into which.

c. Claim 20 recites a process of preparing a compound of formula (I). However, it only recites the step of phosphorylation of an appropriate hydroxyl group of formula (II), which only produces a subset of formula (I) when Z' is hydroxy. It is unclear what steps are intended when Z' is another group (e.g., $-NR^{1'}R^{2'}$).

Claim Objections

3. Claims 11 and 22-24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Said claims recite R^3 with a definite limitation, and thus, do not have the situation of "broad/narrow limitations".

Allowable Subject Matter

4. Claims 12 and 25 are allowable because said claims recite species with A as a pyrazolyl ring, and the 7-position has a phosphate terminal group. Said species are not taught or fairly suggested by the prior art of record.

References cited on PTO-892

5. The references cited on PTO-892 (Mortlock et. al. (US'338); Anderson et. al. (US'518) and Hennequin et. al. (WO'955)) show the state of the art only. While they teach the general core of the instant formula (I), they fail to teach or fairly suggest "*phosphonooxy*" as a substituent on R^1 or on Z.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tamthom N. Truong/

Tamthom N. Truong
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

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4-24-08